REMARKS

Applicant respectfully requests reconsideration. Claims 3, 4, 8-13, 39, 44, 143, 144, 147 and 149 are pending for examination with claims 3, 13, 39 and 44 being independent claims. No claims have been amended. No claims have been canceled or added herewith. No new matter has been added.

Rejections under 35 U.S.C. § 112

The rejection of claims 3, 4, 8-13, 39, 44, 143, 144, 147 and 149 has been maintained under 35 U.S.C. § 112, first paragraph.

In the prior office action (dated May 3, 2005) the Examiner rejected the claims for not reasonably providing "enablement for decreasing mitochondrial membrane potential in a tumor cell *in vivo*." In support of that rejection the Examiner, stated that the claimed methods would result in a "generalized response" affecting "all antigen presenting cells in any part of the body" and because no mechanism for targeting the compounds to tumors is discussed. The rejection has been maintained. Applicant requests that the rejection be withdrawn. The Examiner has not made a prima facie case of lack of enablement. Applicant has asserted, and reiterates here, that the specification was enabling at the time of the invention for the claimed invention. Additionally, the Examiner has misunderstood Applicant's arguments presented in the reply to Office Action mailed by Applicant on November 3, 2005. Each of these points is addressed below.

The Examiner has the initial burden of establishing the reasons for lack of enablement. The Examiner must present evidence or explain why the accuracy of Applicant's assertions are doubtful. See MPEP section 2164.04:

> "In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a

> reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 439 F.2d at 224, 169 USPQ at 370."

In the instant case the Examiner has never once in the lengthy file history (Application filed in 1999) provided an objective piece of evidence or sufficient argument to support a lack of enablement rejection. The only reason provided by the Examiner for his rejection is that HLA-DR will be upregulated on cells other than cancer cells and thus a targeting mechanism for targeting the compounds to cancer cells is required. The relevance of this argument to a lack of enablement is unclear and is not set forth in the Office Action. Additionally, this reasoning is not sufficient to support a rejection for a lack of enablement. Applicant addresses each of these points in more detail below. In order to support a prima facie rejection for lack of enablement, the Examiner must "establish a reasonable basis to question the enablement provided for the claimed invention." (see MPEP section above). This has not been done.

The Examiner stated in the Office Action dated May 3, 2005 (and repeated in its entirety in the Office Action dated February 9, 2006):

> "HLA-DR is a family of HLA class II haplotypes that is not specific to a tumor cell but is specific to the human subject being treated. As such, class II HLA-DR molecules of the same haplotype are expressed on every antigen-presenting cell in that subject's body. Based upon the level of knowledge of the artisan, the artisan would expect that every HLA-DR molecule on every antigen-presenting cell in that subject's body was equally capable of up-regulating expression of HLA-DR and capturing said ligand. Capture would not be limited to the cells of the cancer. Accordingly, rather than inducing a response specifically against the cancer cells, the artisan would predict that more generalized response would be generated in all antigen presenting cells in any part of the body. The claims are not limited to, and the specification does not disclosure a mechanism for, specifically targeting the peptide to the HLA-DR expressing cells of the tumor without allowing normal antigen

presenting cells of the subject to also capture and be affected by the ligand binding to HLA-DR."

This reasoning is misplaced and does not support a lack of enablement of the claimed invention for several reasons. Initially, even if HLA-DR is expressed on antigen presenting cells (APCs) and administration of an HLA-DR inducing agent is sufficient to upregulate HLA-DR on the surface of APCs, it is unclear how this is relevant to a lack of enablement for a method of treating a tumor. The Examiner does not explain in the record the relevance of this fact to a lack of enablement. If HLA-DR is upregulated on APCs that should not have an effect on the upregulation of HLA-DR on tumor cells, as far as Applicant is aware. Claims 3, 4, 8-12, 39 and 143-144 are directed to a method of decreasing mitochondrial membrane potential in a tumor cell by upregulating HLA-DR and contacting the cell with a ligand. The claims do not require that mitochondrial membrane potential is not decreased in other cells such as APCs. Thus, it is unclear why the fact that mitochondrial membrane potential may be decreased in other cells has any relevance to these claims.

The only possible reason that Applicant can surmise for the reasoning provided by the Examiner as a basis for a lack of enablement rejection is that it implies a lack of safety of the method (i.e., side effects). In an effort to be responsive and to try to reply to the Examiner's rejection, Applicant responded to the rejection by arguing as to why the stated reasons did not provide an adequate reason to doubt the safety of the invention.

In the Office Action dated February 9, 2006 the Examiner has stated that "Contrary to Applicant's position, the enablement rejection is not based upon clinical safety, but the fact that the invention as claimed cannot target the specific cells to which the agent is supposed to be directed." (Page 3) This rejection is flawed. The Examiner has stated that "the artisan would expect that every HLA-DR molecule on every antigen-presenting cell in that subject's body was equally capable of up-regulating expression of HLA-DR and capturing said ligand". If the methods of the invention upregulate expression on every cell including tumor cells such that the ligand can bind, then the invention is working as Applicant asserted it does. Claims 3, 4, 8-12, 39 and 143-144 are directed to methods of upregulating HLA-DR expression and subsequently contacting the receptor with a ligand. The fact that other cells are altered during the process has no bearing, as far as

Applicant can determine, on the claimed invention. The Examiner is requested to clarify how the fact that other cells may react to the compounds being administered has any relevance to the fact that tumor cells are also affected by the treatment.

If the Examiner is stating that the compounds must be specifically designed to target tumor cells only, he is incorrect. Applicant has asserted in the specification that the compounds can be administered in vivo and that they will produce an effect (induction of HLA-DR) on tumor cells. The Examiner has apparently created his own step in the method of the invention that requires some active targeting mechanism. No evidence exists in the record to establish that such a step is required. Further the Examiner's own comments ("the artisan would expect that every HLA-DR molecule on every antigen-presenting cell in that subject's body was equally capable of up-regulating expression of HLA-DR and capturing said ligand") suggest that a specific targeting step is not necessary. If the Examiner had a different purpose for his arguments he is respectfully requested to make that reason clear on the record. Applicant cannot make the Examiner's rejections for him.

Furthermore, claims 13, 44, 147, and 149 are not limited to tumor cells. Absolutely no evidence or arguments have been set forth in the record as to why these claims should be rejected. These claims should be allowed immediately. The Examiner has stated in the office action that "the artisan would expect that every HLA-DR molecule on every antigen-presenting cell in that subject's body was equally capable of up-regulating expression of HLA-DR and capturing said ligand". This implies that such claims are enabled. Thus, the reasoning provided in support of the rejection for a lack of enablement, i.e. that Applicant has not taught a method for targeting tumor cells exclusively, does not apply to such claims.

In response to the prior Office Action, Applicant provided sufficient evidence to rebut the rejection of record. Rather than provide any new evidence or sound reasoning to support maintenance of the enablement rejection, the Examiner has reiterated his conclusion that "it would take undue trials and errors to practice the claimed invention and this is not sanctioned by statute". What trials and errors is the Examiner referring to? He has not presented a single argument or piece of evidence to establish that the claimed invention is unpredictable or requires further

experimentation. The Examiner has not met his burden in maintaining the rejection for lack of enablement. Mere conclusions as to whether "trials and errors" are required is not sufficient.

Applicant also asserts that the claims are enabled by the specification as filed. The specification includes a description of the molecules useful according to the invention, provides details on carrying out the methods, asserts that such molecules have utility in these methods and includes data to demonstrate the particular scientific principals. In particular many examples were performed and are described in the specification. For instance, Example 3 is a summary of data demonstrating the relationship between the metabolic state of a cell and expression of MHC class II molecules. This finding is one of the important discoveries leading to the invention. Figure 10 shows ligation of class II molecules on resting, but not activated B cells, results in apoptotic death. Example 3 also includes data demonstrating correlations between surface expression of molecules and type of cell death. Table 5 depicts a summary of this data.

Example 7 includes data analyzing UCP expression in a panel of tumor cells. All of the tumor cells lines examined express UCP intracellularly. Example 7 points out the relationship between these data on UCP expression in tumor cells and shift in subcellular production of ATP from mitochondria to cytosol as cells divide. These data also demonstrated that greater levels of mitochondrial UCP was observed in the drug resistant L1210/DDP cells than in L1210/0 – drug sensitive cells. To determine whether increased UCP corresponded to increased mitochondrial proton leak and a lower mitochondrial membrane potential the characteristics of non-phosphorylating respiration in intact L1210 wild type and L1210 DDP cells was assessed and the results were presented in Figure 16. Mitochondrial membrane potential in DDP cells was significantly lower than in wild type cells and state 4 oxygen consumption in DDP cells was significantly higher than in wild type cells, indicating increased mitochondrial proton leak.

Example 8 includes data on the rates of glucose utilization, oxidation and cell surface and intracellular Fas levels in Melanoma Cells. In particular, Figure 18 depicts the rates of glucose utilization and oxidation in B16 melanoma cells. Both glucose utilization and glucose oxidation decreased with increasing concentrations of sodium acetate, demonstrating a correlation with expression of cell surface Fas in the same cells (as shown in Figure 17).

Example 10 describes the use of fatty acids as a mitochondrial carbon source. For instance, Figure 21 demonstrates that the L1210 DDP (resistant cells) use oleic acid at much higher rates than the L1210 cells. The data also demonstrate that class II engagement results in increased cAMP (necessary for UCP activity) and that the mitochondrial membrane potential of L1210DDP (resistant) cells is lower than L1210 cells.

Example 12 demonstrates that Sodium Acetate (a mitochondrial modifying agent) increases cell surface Fas expression in both cell lines. Additionally, the data indicate that in a dose dependent manner, culture of both cell types with acetate results in susceptibility to Fas-dependent cell death.

The combination of these changes described in the examples and the specification was adequate to demonstrate to one of skill in the art at the time of the invention that first inducing HLA-DR expression and then engaging the HLA-DR molecule with a ligand is sufficient to decrease mitochondrial membrane potential in the cell. Applicant asserts that a correlation between the data presented in the specification for the molecules of the invention and their use in decreasing mitochondrial membrane potential in a cell in vitro or in vivo is disclosed and enabled.

MPEP section 2164.02 teaches that

> "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).
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> Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985)"

Applicant has presented data and asserted that it correlates with the scope of the claimed invention. The Examiner has not presented any evidence or even any reasoned arguments to demonstrate why it does not correlate other than broad conclusory statements that the "specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims." These types of statements are not sufficient to rebut Applicant's assertions.

In view of the teaching of the instant application and the state of the art at the time of filing, Applicant submits that the claimed invention can be practiced without undue experimentation. Applicant has provided compounds that induce HLA-DR and compounds that are ligands thereof and have provided guidance to one of ordinary skill in the art to use these compounds to decrease mitochondrial membrane potential. Therefore, the amount of experimentation required to practice the invention is not undue. One of ordinary skill in the art would be able to administer the claimed compounds of the invention using no more than routine experimentation with Applicant's disclosure in hand.

Examiner's reply to Applicant's arguments.

Applicant presented arguments in response to the Office Action mailed from the USPTO on May 3, 2005. In the current Office Action, mailed February 9, 2005, the Examiner addressed Applicant's arguments. It is Applicant's belief that the Examiner has misunderstood Applicant's arguments. Applicant wishes to clarify on the record the purpose and scope of those arguments.

As discussed above, Applicant believed that the Examiner was making a rejection based on a lack of safety. In response to the rejection Applicant argued that even if safety were relevant to the issue of enablement, at least one of the drugs that are within the class of HLA-DR agents listed in the specification has been administered systemically to patients and thus safety should not be a concern. Specifically it was argued

> "For instance, the class of inducing agents includes adriamycin. A discovery of the invention lies in the identification of the induction of the cell surface molecule by regulating the intracellular dissipation of proton motor force using the claimed inducing agents. The cell can then be contacted with the ligand to decrease membrane potential. As far as Applicant is aware, these latter steps were not previously recognized in the art. However, as stated above some inducing agents, such as adriamycin (which, according to the teachings of the invention, has the same biological effects on MHC HLA-DR expression as the inducing agents specifically listed in claims 3 and 39), have previously been administered systemically to patients. Thus, the safety problem proposed by the Examiner in the office action has not proven to be a real safety problem that would prevent the systemic administration of an HLA-DR inducing agent."

The Examiner has replied by stating that "Applicant attempts to bolster the argument of enablement by pointing out the clinical use of ADRIAMYCIN.....Accordingly, ADRIAMYCIN could be considered preferential in its targeting of tumor cells. The same could not be said for the agents of the instantly claimed invention. ADRIAMYCIN is structurally and functionally distinct from the agents of the instantly claimed invention..... Merely equating an observed *in vitro* effect of ADRIAMYCIN to an observed *in vitro* effect of the agents recited in claims 3 and 39 does not translate into a comparison of *in vivo* delivery of the agents."

Applicant has not argued that an in vitro effect of ADRIAMYCIN could "translate into a comparison of *in vivo* delivery of the agents". Applicant argued that ADRIAMYCIN, which is an HLA-DR inducing agent of the invention is administered to human subjects in order to demonstrate that any safety concerns of this class of molecules is minimal.

Accordingly, withdrawal of the rejection of claims 3, 4, 8-13, 39, 44, 143, 144, 147 and 149 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

In view of the above amendment, Applicant believes the pending application is in condition for allowance.

Respectfully submitted,

By _____

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